REMARKS

The title of the application is amended to: METHOD FOR ATTACHING BIOLOGICAL MOLECULES TO A GLASS SURFACE. In addition, the originally filed abstract is replaced by the abstract attached. Support for these amendments is found at page 44, line 20 through page 50, line 14.

Claims 1, 14, 23 and 25 are amended to recite that the end-capped group reacts with a biological molecule. Support is found in the specification at page 47, lines 21-23, and in Figures 11 and 12.

As suggested by the Examiner, Claim 6 is amended to recite "nucleic acids" rather than "nucleic acid sequences."

New Claim 27 is dependent on Claim 14 and specifies that the glass surface is a microscope slide surface. Support is found throughout the specification, for example at page 43, lines 7-8, and in originally filed Claim 7.

No new matter has been added.

For clarification purposes, Applicants respectfully note that the document filed on October 30, 2003 was a Reply to Restriction Requirement rather than a Preliminary Amendment.

The remainder of these remarks is set forth under appropriate headings for the convenience of the Examiner.

Rejection of Claim 6 under 35 U.S.C. §112, second paragraph

Claim 6 is rejected under 35 U.S.C. §112, second paragraph. Specifically, the Examiner stated that a nucleic acid sequence is grouped incorrectly with proteins, peptides and carbohydrates.

As amended, Claim 6 includes a group that consists of "proteins, peptides, nucleic acids and carbohydrates."

Therefore, present Claim 6 meets the requirements of 35 U.S.C. §112, second paragraph.

Advantages of Applicants' Claimed Invention

Applicants' claimed invention relates to a method for attaching a biological molecule to a glass surface. The method includes reacting the end-capped amino group on a silane-treated glass surface, e.g., a microscope slide, with a phosgene equivalent, such as, for example, a carbonyl diimidazole or methyl ethyl ketone oxime carbonate. The reaction results in a protected isocyanate group or a protected group having the formulae set forth in Claims 14 or 25, specifically, >N-C(O)-N< or >N-C(O)-O-N<.

Compared to reactants such as diisocyanates or monomeric polyisocyanates, the claimed phosgene equivalent has higher reactivity under milder conditions and does not result in crosslinking to surface-bound amino groups. See, for example, page 46, line 26 through page 47, line 2 and page 47, lines 12-20 of the specification. In addition, as discussed at page 47, line 21 through page 49, line 12 of the subject application, the reaction with the phosgene equivalent results in a protected group that is stable in the presence of moisture, resulting in slides less susceptible to moisture-induced degradation and longer shelf life.

While generally stable in the presence of water at room temperature, the protected group reacts with amine, hydroxy or carboxyl groups found in biological molecules, forming a covalent bond and attaching the biological molecule to the glass surface.

Further discussion of protected isocyante groups in attaching molecules such as peptides to glass surfaces is found in the article *A Water-Stable Protected Isocyanate Glass Array Substrate*, by S. R. Sompuran, *et al.*, Analytical Biochemistry (2004) (Reference AX4), submitted with a Supplemental Disclosure Statement filed concurrently herewith.

Rejection of Claims 1, 14, 23 and 25 under 35 U.S.C. §103(a)

Claims 1, 14, 23 and 25 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sakurai *et al.* (U.S. Patent No. 4,526,921) in view of Butterfield *et al.* (U.S. Patent No. 6,017,522).

The Examiner stated that Sakurai *et al.* teach that isocyanate groups increase the adhesive strength of a silane-treated glass surface and that Butterfield *et al.* teach that the amine groups on proteins or biological molecules can react with isocyanate groups to form a covalent bond. The Examiner also stated that Butterfield *et al.* teach that the isocyanate may be end-capped. The

Examiner further stated that one of ordinary skill in the art would have combined the two references for the advantage of an improved glass surface capable of binding biological molecules.

Applicants respectfully disagree.

Sakurai *et al.* is directed to a rigid acetal resin composition having improved surface gloss and weather resistance, suitable for making metal substitutes for machinery or automobile exterior parts. The acetal resin composition includes inorganic fillers, listed, for instance, at Col. 6, lines 28-38 of the reference:

> The inorganic fillers that can be used in the present invention include powderous, flaky or fibrous metals, metal oxides, metal hydroxides, metal sulfates, metal sulfides, metal carbonates, metal silicates including glass fibers or glass powders, metal borates, potassium titanate, carbon or graphite. In particular, the preferred inorganic fillers include glass fibers, glass powders, silica, talc, alumina, mica, clay, dawsonite, montmorillonite, carbon fibers, potassium hexatitanate fibers, zinc oxide, calcium oxide, calcium carbonate, etc.

As discussed at Col. 1, lines 63-66 of Sakurai *et al.*, isocyanates can improve "adhesiveness between silane-treated glass fibers or glass powders and acetal resins." See also Col. 5, lines 13-19, of Sakurai *et al.*:

> Further, it is also hitherto known that an isocyanate or polycarbodiimide is added as a coupling agent in order to increase adhesive strength of the acetal resin with the fillers, but these coupling agents generally adversely affect the heat stability of the acetal resin and also markedly color the resulting polymer or contaminate a mold.

Sakurai *et al.* do not disclose or suggest Applicants' claimed method for attaching a biological molecule to a glass surface. The reference does not disclose or suggest reacting an end-capped amino group on a silane-treated glass surface with a phosgene equivalent (*e.g.*, a carbonyl diimidazole or a ketoxime carbonate) to form a protected isocyanate group, as specified in Claims 1 and 23. Nor do Sakurai *et al.* disclose or suggest reacting an end-capped amino

group on the silane-treated glass surface with a phosgene equivalent to form an end-capped group that includes a functional group represented by the structural formulae set forth in Claims 14 and 25. There is no disclosure or suggestion in Sakurai *et al.* for reacting the protected isocyanate group or end-capped group with a biological molecule, thereby forming a covalent coupling and attaching the biological molecule to the glass surface.

It is respectfully noted that the Examiner has provided no evidence regarding how filler treatment with an isocyanate coupling agents, described by Sakurai *et al.* in the context of acetal resins, relates to the specific reactions (employing a phosgene equivalent and forming a protected or end-capped group) that are claimed by Applicants.

In contrast to biological molecules which, as discussed at page 47, lines 21-23 of the subject application, include groups such as amino, hydroxy or carboxyl, acetal resins have a linear formula of the type -O-CH_2-O-CH_2=CH_2-, as seen on the attached page from Hawley's Condensed Chemical Dictionary, 12th ed. Van Nostrand Reinhold, 1993 (Exhibit 1). The Examiner has provided no evidence for how increasing adhesive strength between a glass fiber or glass powder particle and surrounding acetal polymer, disclosed in the reference, relates to covalently coupling biological molecules to a glass surface.

There is no recognition or appreciation in Sakurai *et al.* of the problems addressed and solved by Applicants' claimed invention. For instance, whereas Applicants' concerns relate to crosslinking of diisocyantes across silane-treated glass surfaces, isocyanate-related problems addressed by Sakurai *et al.* pertain to polymer heat stability, color properties and mold contamination. Whereas Applicants' claimed protected group, formed using a phosgene equivalent, improves stability and storage shelf life in the presence of moisture, the cited reference addresses surface gloss and weather resistance properties of a rigid acetal resin composition.

In addition, Applicants respectfully note that the reference teaches away from a silane-treated glass surface, as seen at Col. 4, line 66 through Col. 5, line 12:

> In particular, when various fillers are mixed with acetal resins to produce composite materials according to the conventional processes, the surface of the filler should be previously treated with a silane treating agent, such as aminosilane, vinylsilane,

> epoxysilane, etc., an organic titanate, a fatty acid or a fatty acid salt. To the contrary, such a pretreatment of various fillers is not necessarily essential in the present invention. In other words, upon mixing the acetal resin and the fillers, the low molecular weight polycarbonate compound can be merely dry blended therewith, and the resulting mixture can be melt-extruded simultaneously. It is possible, as a matter of course, to use the pretreated fillers as described above in the composite materials of the present invention.

Thus the reference neither discloses nor suggests Applicant's invention as set forth in Claims 1, 14, 23 and 25.

Butterfield *et al.* do not remedy the deficiencies of Sakurai *et al.*

Butterfield *et al.* describes reactive poly(alkylene oxides) that are reacted with chelating agents such as diethylenetriaminopentaacetic acid (DTPA), or precursors thereof, to form metallizable segmented polymers. When associated with metal ions, the resulting segmented polymers form imaging or cytotoxic agents. Agents that include gadolinium ion (Gd^{3+}), for example, can be used in magnetic resonance imaging of the human body.

As set forth in formula 1, the reference teaches a divalent poly(alkylene oxidylene) moiety, having a carbon terminus at R, where R can be an immunoreactive group (e.g., antibody, DNA, DNAase and others). Reactive poly(alkylene oxidyl) species are listed at Col. 15, lines 56-66 of Butterfield *et al.* and include poly(alkylene oxidyl) isocyanates. The reference teaches that poly(alkylene oxidyl) species may be either functional at both ends or functional at one end and end-capped at the other, as seen at Col. 15, line 66 through Col. 16, line 6. Specific examples of end-capped or protecting groups provided by Butterfield *et al.* include ether, acyl, trityl or trimethoxy trityl groups. (Col. 16, lines 1-4.) The reference further teaches that the protecting groups (end caps) can be removed "to permit reactions to produce amine or carboxyl moieties." (Col. 16, lines 4-6.) At Col 14, line 50 through Col. 15, line 40, Butterfield *et al.* set forth oxidylene examples of linking group precursors to form a linking between the terminus of poly(alkylene oxidylene) and R. As seen at Col 14, lines 52-64, the examples include isocyanato groups.

In addition, at Col. 15, lines 13-40, Butterfield, *et al.* teach crosslinking agents including biisocyanates:

> A group that can be linked to the protein or biological molecule containing the immunoreactive group, or to the modified protein as noted in (1) and (2) above by use of a crosslinking agent. Certain useful crosslinking agents, such as, for example, difunctional gelatin hardeners, bisepoxides and bisisocyanates become a part of, i.e., a linking group in, the protein-segmented polymer complexing agent conjugate during the crosslinking reaction. Other useful crosslinking agents, however, facilitate the crosslinking, for example, as consumable catalysts, and are not present in the final conjugate. Examples of such crosslinking agents are carbodiimide and carbamoylonium crosslinking agents as disclosed in U.S. Pat. No. 4,421,847 and the dication ethers of U.S. Pat. No. 4,877,724. With these crosslinking agents, one of the reactants must have a carboxyl group and the other an amine, alcohol, or sulfhydryl group. The crosslinking agent first reacts selectively with the carboxyl group, then is split out during reaction of the "activated" carboxyl group with, for example, an amine to form an amide linkage between the protein or cytotoxic agent and the segmented polymeric chelating agent, thus covalently bonding the two moieties. An advantage of this approach is that crosslinking of like molecules, e.g., proteins with proteins or complexing agents with complexing agents, is substantially avoided where the agent has one reaction site, whereas the reaction of difunctional crosslinking agents is less selective and unwanted crosslinked molecules can be obtained. Especially preferred protein reactive groups include amino and isothiocyanato.

The reference neither discloses nor suggests attachment to a glass surface. It does not address, nor suggests coupling of biological molecules to glass.

As with Sakurai *et al.*, Butterfield *et al.* neither disclose nor suggest reacting an amino group (on a silane-treated glass surface) with a phosgene equivalent. Nor do Butterfield *et al.* disclose or suggest that the reaction with the phosgene equivalent results in the formation of a protected isocyanate group or the formation of an end-capped group having the structural formulae set forth in Claims 14 and 25. Butterfield *et al.* do not disclose or suggest that the group that reacts with a biological molecule is the group formed by the reaction with the phosgene equivalent .

As with Sakurai *et al.*, there is no recognition or appreciation in Butterfield *et al.* of the problems faced by Applicants. As discussed above, Applicants' recognized that both isocyanate functional groups in a diisocyanate can react with surface bound amino groups, thus reducing the numbers of free isocyanate groups available to react with the biological molecule to be attached to the glass surface. As a result, Applicants react an end-capped amino groups on the silane-treated glass surface with a phosgene equivalent. In contrast, the crosslinking problem recognized by Butterfield *et al.* is that of crosslinking between proteins with proteins or complexing agents with complexing agent. (See Col. 15, lines 34-40.) As a solution, the reference recommends protein reactive groups that include amino or isothiocyanato groups.

Thus neither reference, alone or in combination discloses or suggests Applicants' claimed invention. Specifically, neither Sakurai *et al.*, nor Butterfield *et al.*, taken separately or in combination disclose or suggest a method for attaching a biological molecule to a glass surface that includes reacting an end-capped amino group on a glass surface with a phosgene equivalent to form a protected isocyanate group or an end-capped group having the structural formulae shown in Claims 14 and 25; and reacting the group with a biological molecule, thereby forming a covalent coupling and attaching the biological molecule to the glass surface.

Therefore, Claims 1, 14, 23 and 25 are patentable over Sakurai *et al.* in view of Butterfield *et al.*

Claims 2-7, 15-19 and 27

Applicants acknowledge that Claims 2-5, 7, 15-19 and amended Claim 6 would be allowable if rewritten to include all the limitations of the base claim and any intervening claims.

Newly presented Claim 27 depends on Claim 14 which, as discussed above, is patentable over Sakurai *et al.* in view of Butterfield *et al.* Furthermore, Claim 27 is similar in format to Claim 7, which would be allowable if rewritten. Therefore, Claim 27 also is patentable over Sakurai *et al.* in view of Butterfield *et al.*

Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested. In addition, Applicants respectfully

request the Examiner to initial the references AS3, AT3 and AU3 on PTO Form 1449, filed on filed August 13, 2002.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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